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REVIEW

Effects of home wall painting on respiratory and allergic diseases in children

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ABSTRACT

The effect of household air pollution on health is an important topic of study and research considering the increasing amount of time that people spend inside buildings. Although numerous studies have been conducted on indoor allergens and their effects on the development of allergies in both adults and children, little is known about the pollutants produced by indoor painting and their association with respiratory diseases.

Recent studies have suggested a significant cause-and-effect correlation between high VOCs concentrations in indoor air, due to repainting, and the development of respiratory and allergic diseases in children, while other papers report the absence of effects on health when paints with low VOCs concentrations are used. However, the evidence is currently insufficient to draw firm conclusions, and further high-quality observational studies, as well as clinical trials, are needed for a more comprehensive investigation to elucidate this issue.

Given the potential risks in both the development of fetuses and children, it is imperative that government agencies and organizations implement proactive measures on wall paints to prevent potential adverse health outcomes.

IMPACT STATEMENT: Little is still known about the correlation between air pollution due to indoor wall painting and the development of allergy and respiratory diseases in children. Many components derived from paints can stimulate the airways, particularly in children. Proactive initiatives are necessary to protect fetuses and children from these indoor pollutants.

INTRODUCTION

During the last decades, the life of people has experienced profound transformations caused by industrialization, urbanization, and fuel fossils consumption. All these factors have led to a dramatic increase in air pollutants, including particulate matter (PM), nitrogen dioxide (NO_2), ozone (O_3), affecting both human health and the entire ecosystem (1).

With the increasing concentration of air pollutants, it has also been registered a rapid increase in the prevalence of allergic diseases, such as asthma, allergic rhinitis, atopic dermatitis and food allergies.

Notably, childhood asthma is emerged as a pressing public health concern, with compelling evidence suggesting its potential to persist into adulthood and even develop into chronic obstructive pulmonary disease (COPD) (2).

ABBREVIATIONS LIST

AD: Atopic Dermatitis; CI: Confidential Interval; COPD: Chronic Obstructive Pulmonary Disease; EEA: European Environment Agency; EJ: Environmental Justice; EPA: Environmental Protection Agency; IAC: Indoor Air Comfort; IAQ: Indoor Air Quality; IED: Indoor Environments Division; HDM: House Dust Mites; MIT: Methylisothiazolinone; OR: Odd Ratio; TEAM: Total Exposure Assessment Methodology; TVOCs: Total Volatile Organic Compounds; VOCs: Volatile Organic Compounds.

KEY WORDS

Wall paint; allergy; respiratory diseases; children; VOCs.

While many studies focused on infectious agents and on allergens in the domestic environment, such as proteins derived from mites, cat, dog, cockroaches and fungi, the need to prevent the development of asthma and allergic diseases in children has stimulated research into other potential indoor and outdoor environmental causes (3), such as volatile organic compounds (VOCs), namely a group of molecules having at 293.15 K a vapor pressure of 0.01 kPa or more (4). Household products, such as glues, cleaners, and paints, have been identified as significant contributors to indoor air pollution, releasing VOCs and other chemical molecules that may have adverse health effects (3, 5). Even though children spend the majority of their daily time indoors (6-8), nowadays there is insubstantial knowledge about chemical indoor pollutants and their correlation with diseases developed during childhood. Actually, a limited number of studies explore the potential correlation between chemicals or fine particles emission resulting from painting walls and the possible effects on respiratory and allergic diseases in children (9, 10), and even less studies take in account the correlation between VOCs concentration in the paint with health diseases, whereas paint companies have already started to offer products with lower VOCs concentration. The aim of this paper is to review the latest scientific medical literature on the effect of home wall painting or repainting on respiratory and allergic diseases, such as asthma, atopic dermatitis and rhinitis, in children.

METHODS

Databases and keywords

PubMed, Embase and Cochrane databases have been used to find the most relevant studies conducted within the last 16 years (from 2006 to 2022).

The keywords used were: “indoor wall painting”, “indoor wall repainting”, “indoor wall paints AND allergy AND children AND airway disease”.

The articles have been selected with the following criteria:

– publications in scientific medical journals with peer-review;
– papers including, among the objects of the study, also the components of the internal wall paintings of the houses;
– papers including mould and moisture in indoor environment;
– papers studying the correlation between components of internal wall paints and respiratory and/or allergic diseases;
– paper identifying the risks with “Odd ratio” (OR) and confidence interval (CI);
– relevant papers identified from citation searching;
– articles relating to the “sick building syndrome” have been excluded because they are much discussed as a nosological entity and not recognized as such by some authoritative scholars;

RESULTS

With these criteria, 251 publications were extracted and among them 34 were in compliance with the inclusion criteria. The selection criteria are detailed following PRISMA guidelines in flowchart of **Figure 1**.

Amongst the studies which have been more accurately analyzed for their content, there were:

– 15 epidemiological or cohort studies, among them the most relevant have been reported in **Table 1**;
– 10 reviews, among them the most relevant have been reported in **Table 2**;
– 3 studies on the evaluation of indoor air quality and 1 on “green homes”;
– 4 publications on indoor air quality (IAQ) and Atopic Dermatitis (AD) (**Table 3**).

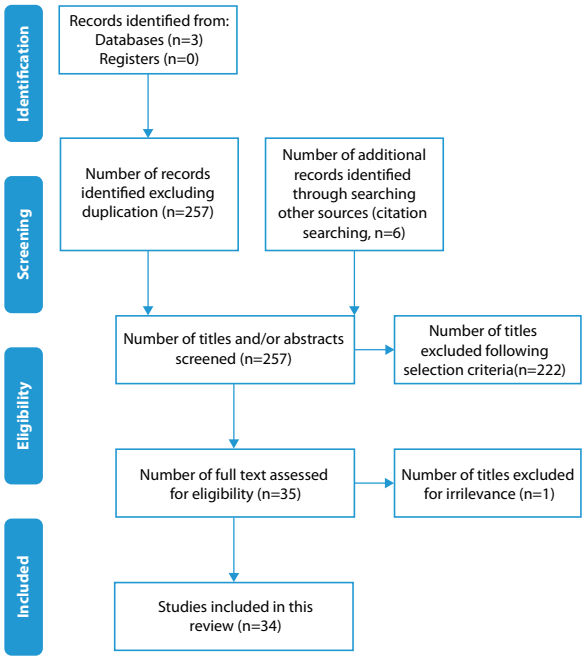

Figure 1. *PRISMA flowchart.*

This is a narrative review and no meta-analysis has been performed. However, in order to be more informative, odds ratios and CI of the health outcomes associated with environmental exposure for the selected studies have been reported.

INDOOR AIR POLLUTANTS

From the analysis conducted by the selected articles, it emerged that the most frequent indoor air pollutants are: moulds, VOCs (volatile organic compounds), PEGs (polyethylene glycols), and isothiazolinones (**Table 4**).

Table 1. *Most significant Cohorts and multi-center studies.*

No of subjects	Pollutant	Effects	Results	Ref.
10,851 children	VOCs (PEG)	Asthma, hyperhidrosis	OR = 2.779 (CI = 1.33-5.80) *	#7
31,742 children	Mould	Asthma, allergic rhinitis	OR = 1.18 (CI = 1.09-1.28)	#12
863 children	VOCs	Allergy to HDM	OR = 1.40 (CI = 1.10-5.30)	#16
172 children	Low VOCs (PEG)	Wheezing, asthma	OR = 1.16 (CI = 1.03-1.29)	#23
462 students	Para-dichloro benzene	Asthma	OR = 1.16 (CI = 1.06-1.27)	#26
163 children	VOCs from paint	Asthma attacks	OR = 10.49 (CI = 1.16-94.85)	#27
1048 students 12-15 years old	Unspecified	Asthma	OR = 1.71 (CI = 1.60 – 2.7)7	#28
235 partecipants	Green homes	Diminished risk of asthma	Asthma: OR = 0.34 (CI = 0.12-1.00) Less asthmatic attacks: OR = 0.31 (CI = 0.11-0.88) Less absence from school due to asthma: OR = 0.21 (CI = 0.06-0.74)	#30

* This data refers to the exposition to wall paint.

Table 2. *Most relevant reviews.*

No of studies	Pollutant	Effects	Ref.
48	VOCs	Asthma and allergy in children and adults, no clear conclusions	#5
61	Moulds	Asthma (OR = 1.49; CI = 1.28-1.72), wheezing (OR = 1.68; CI = 1.40-1.90) allergic rhinitis (OR = 1.39; CI = 1.28-1.51)	#8
21	Aldehydes, aromatic hydrocarbons, aliphatic hydrocarbons, other VOCs	Exacerbation of asthma and irritation of the lower airways, in children and adults	#10
37	VOCs and S-VOCs	Childhood bronchial asthma	#13
20	VOCs	Uncertainty about the effect of most VOCs as cause or aggravating agent of asthma in children and adults	#21
53	VOCs	Weak evidence that VOCs have a role in the development of asthma and allergic diseases in adults and children and in their exacerbations	#22
17	VOCs	VOCs that could favour allergic and respiratory diseases	#32

Table 3*. Most relevant studies on indoor air quality and Atopic Dermatitis (AD).*

No of subjects	Redecoration activities	Effects	Results	Ref.
20,687 children	House painting during pregnancy	Increase risk of AD	Renovation: OR = 1.61 (CI = 1.27-2.02) House painting: OR = 1.72 (CI = 1.30- 2.24)	#31
51 children	Paintings and furnishings in hospital wards	Increase symptoms of AD	Low pollutants rooms: SCORAD reduced from 42 ± 11.5 to 29.8 ± 8.9	#33
2536 children	Painting, floor covering and new furniture	Increased risk of allergic diseases and AD	Allergy: OR 1.8 (CI 1.3-2.6) Eczema: OR 1.9 (CI 1.4-2.7)	#34

Table 4. *Common VOCs emitting from paints.*

VOC classes	Molecules
Alcohols	3-octanol, isobutanol, 1,2-propandiol, Texanol, butanol
Aldehydes	Acetaldehyde, benzaldehyde, formaldehyde
Hydrocarbons - aromatic	Benzene, styrene, xylene, toluene, ethylbenzene, naphtalene, chlorobenzene
Hydrocarbons - aliphatic	Heptane, decane, undecane, haxane, nonane, dodecane
Esters	2,2,4 – trimethyl – 1,3-pentanediol monoisobutyrate, 2-(2- butoxyethoxy)-ethanol acetate
Glycols	Propylene glycols ethers (PEG), butyldiglycol
Biocides	5-chlor-2-methyl-4-isothiazolin-3-on (CIT), 2-methyl-4-isothiazolin-3-on (MIT)

Moulds

Moulds are frequent indoor air pollutants, in particular in popular buildings. Their presence can be related with health diseases, and it is a main cause for wall repainting.

Borchers *et al*. reported in their study (11) that moulds can be a cause of allergy and for asthmatics can potentially exacerbate their asthma. The moulds considered for “outdoors” were the *Alternaria* and the *Cladosporium*, those considered for “indoor” environment were the *Penicillium* and the *Aspergillus*.

A meta-analysis was conducted on studies regarding exposure to mould and moisture in homes in relation to asthma and allergy. Data was collected through questionnaires from eight cohorts of children born in Europe. The questionnaires from 31,742 children were analyzed and the results showed that exposure to visible mould and/or moisture during the first two years of life was associated with an increased risk of developing asthma in young children (0-2 years) and allergic rhinitis in children of school age (6-8 years) (12).

Another meta-analysis of observational studies with the aim to research the association between domestic mould, asthma and allergy in children, took into consideration 61 scientific publications. Visible moulds were associated with asthma, wheezing and allergic rhinitis (13).

A Cochrane review in 2015 regarded some studies dealing with the preventive effect of removing moisture and mould from private homes/schools/offices on airway symptoms, airway infections and asthma in adults and children. The authors have included 12 studies, affecting 8028 participants. They found moderate to very low-quality evidence that repairing mould-damaged houses and offices leads to a decrease of asthma-related symptoms and respiratory infections in adults compared to no intervention. The evidence that repairing schools did not significantly change respiratory symptoms in staff is very low-quality although pupils’ visits to physicians due to a common cold were less frequent after remediation of the school (14).

A review of 228 papers (37 out of them summarized in Tables) published in 2011, highlighted the environmental factors that can favor childhood asthma in industrialized countries. According to this analysis, the exposure to environmental tobacco smoke, living in homes close to busy roads, or in damp homes with visible moulds were found to be the most consistent factors associated with asthma in childhood (15).

Volatile Organic Compounds (VOCs)

In many studies, Volatile Organic Compounds, are reported as important components of painting, related to indoor air quality issues.

In Tasmanian, Australia, a study was carried out on a cohort of 962 children, of which 71.3% were males. The authors evaluated the impact of the environment where children used to sleep on the occurrence of asthma and/or wheezing when the children reached the age of 7, concluding that several environmental factors, including heating, painting walls, blankets and sheepskins, in addition to allergens, increase the risk of asthma.

In particular, it was observed an enhancement of the effect on wheezing within 12 months from the painting, probably due to the releasing of VOCs in the air. These data, which show the likelihood that in children allergic to house dust mites (HDM) VOCs could increase airway inflammation (16), confirm the results reported in three other publications cited by the authors (17-19).

A very detailed review of the effects of interior water-based paints on asthma was published in 2013 by a

group of London researchers (20). 13 epidemiological studies were analyzed, 11 in children and adolescents and two in adults, with a population ranging from 153 to 13,988 subjects depending on the study. Most of the studies were done in Europe, two in Australia, three in China and one in Japan. Two studies measured VOCs in houses in which the walls were recently painted revealing high values of organic solvents in air. High levels of aliphatic compounds (C8-C11) of 2,2,4-trimethyl 1,3-pentanediol diisobutyrate (TXIB) and butanol were also detected in recently repainted residences. A systematic review by Canova (21), on the effect of domestic paints on people with and without asthma symptoms demonstrated uncertainty about the effect of most VOCs as a cause or aggravating agent of asthma and underlined the importance the use of adequate ventilation during and after each new painting work and the importance that low-VOCs emission paints have to be developed and disseminated in Europe. In a relevant review of 2007 from Mendeel (10), in the 21 selected papers it was found out that organic chemical pollutant sources in household air could be multiple. In fact, aldehydes (formaldehyde), aromatic hydrocarbons (benzene, toluene, styrene, ethylbenzene, naphthalene, chlorobenzene, dichlorobenzene), aliphatic hydrocarbons (hexane, decane, nonane, undecane, dodecane), other VOCs such as trichloroethylene, tetrachloroethylene, limonene, and finally phthalate esters were detected in the domestic ambient air. Formaldehyde was considered the most important causative agent of possible effects on airway. Although modern water-based and solvent-based paints contain only a few of the substances mentioned above, newly painted walls have been reported in six publications as a risk factor for asthma exacerbation and lower airway irritation in both children and adults.

In a 2014 paper on exposure to VOCs related to asthma and allergy in children and adults, the authors reviewed 225 scientific publications. They reported that the most investigated VOCs classes are: total VOCs, aliphatic compounds, aromatic compounds, microbial and aldehydes, including the formaldehyde, which was the most studied substance. Overall, the evidence is insufficient to arrive at firm conclusions and new high quality and observational studies, as well as clinical trials, on exposure to domestic VOCs and their effects on asthma/allergy would be necessary in order to reduce exposure to VOCs of children and adults with asthma (5).

In 2015, a systematic review on VOCs and risk of asthma and allergy was done by a group of Anglo-American scholars. 53 studies were included in the review. Aromatics (*i.e.*, benzenes, toluene and xylenes) and formaldehyde were the main VOC classes studied, both in relation to the development and the exacerbations of asthma and allergy. Most of these studies had a high risk of "bias" and the review demonstrated that there is weak evidence that VOCs have a role in the development or exacerbation of asthma and allergic diseases in adults and children (22).

A study from South Korea has shown that painting the walls of 17 classes (affecting a total of 172 children) with low VOC content water-based paints did not aggravate asthma and allergic diseases of the children (9).

Polyethylene glycols (PEGs)

PEGs are widely used as co-solvent/additives in water-based paints, and it has been demonstrated that they have an effect on the endocrine system (reproductive system) in animal and in humans (20). However, further experimental models should be developed to clarify the mechanism by which VOCs act on the airways and reproductive and/or endocrine systems. In order to analyze the relationships between common chemicals detected at home and allergy risk, in a Swedish study modified ISAAC questionnaires were collected from the families of 10,851 children aged 1-5 years. Medical examinations and checks of the domestic environment were made in about 10% of the cohort through nursing staff and dust samples were collected from their homes to be analyzed. Of the various chemicals analyzed (aldehydes, alkanes, aromatic hydrocarbons, dimethyl alkanes, PEGs, methyl alkanes, organic acids and texanol), only PEGs were reported to increase the risk of asthma, rhinitis and eczema in a statistically significant way when present in ambient air (19).

Other studies on household air pollutants were focused on PEGs since these molecules appear to promote asthma, eczema and rhinitis in children. PEGs concentration in the ambient air depends on when the room has been painted and also on the cleaning of the house with water. These data were gathered in a Swedish work done on 390 preschoolers' homes and it was found that the

presence of humidity maintains the effect of the PEGs even months after the application of the paint (23).

Isothiazolinones

Isothiazolinones are used for antimicrobial effect in paints. In a 2014 European multicenter study, the authors assessed the amount of methylisothiazolinone (MIT) and related isothiazolinones. A total of 71 wall paints were bought randomly from different supermarkets across 5 European countries and MIT was found in 93% of the paints, with concentrations ranging from 0.7 to 180.9 ppm. The conclusion of the study was that the use of these substances is widespread in European countries. Greater control of these substances in paints is needed to prevent the allergic contact dermatitis they cause in workers (24) and, although the international rules have become increasingly restrictive on the use of these biocides, a more recent paper by the same authors highlighted that the presence of such toxic substances in paintings does not seem to be decreasing in Europe (25).

REPAINTING

Home interior painting has been associated with an increased risk of asthma in different studies (26-27). Asthma symptoms and respiratory infections were investigated by submitting a questionnaire on health to 462 students from 8 upper secondary schools in Malaysia while different pollutants were measured inside and outside the schools, finding a correlation between wheezing and recent indoor painting at home (26).

In another study, children with asthma exacerbation related to home paint exposure were screened using a cross sectional study design in which 163 children, coming from two general pediatric clinics, were included. Also in this case, the results demonstrated that home paint exposure is a significant risk factor of asthma attack (27).

Furthermore, in a recent study made in China on sleep disorders in children aged 3-14 years with and without allergic rhinitis were taken in account the characteristics of the interior environment. 427 children with allergic rhinitis and 1046 control children participated in the study and the outcome has been that emulsion paints and tobacco exposure in early childhood can be associated with hyperhidrosis during sleep (7).

Another research, which used ISAAC questionnaire, evaluated the risk of asthma and respiratory symptoms among 1056 students aged 12-15 years based on the air quality in their home and school environment. In particular, the results showed that the risk was significantly higher when the rooms of their house were recently repainted (28), an observation that is in accordance with the results reported in a previous review by Mendell M.J. (10).

INDOOR AIR QUALITY

A concept that is emerging is “Green buildings and Health”, *i.e.,* houses with high technology of heating and humidity control, located in places with respect for nature, where both indoor and outdoor paints play a fundamental role in maintaining air quality at levels appropriate to individual and public health (29). In a paper published in 2015, the correlations between “green homes” and the risk of asthma in children have been evaluated. In fact, using a questionnaire in a group of Boston families, the researchers have found that children of families living in “green homes” had less risk of asthma symptoms, less risk of asthmatic attacks and less absence from school due to asthma than children living in conventional houses (30).

ATOPIC DERMATITIS

Atopic dermatitis affects millions of people worldwide, often begins in early childhood and can persist into adolescence and adulthood. While the exact cause of this condition remains unclear, recent studies explored association between IAQ and AD.

A study evaluated the incidence of Atopic Dermatitis (AD) at 7 months of age in a cohort of children in Taiwan. 20,687 children had participated in the study. The analysis of the questionnaires distributed to parents demonstrated significant risk factors for the appearance of AD in children, in addition to parental atopy, related to renewal and new painting of the house during pregnancy (31).

A less substantial review analyzed if there is a correlation between allergic disease, air pollution and genetic predispositions. Authors have cited 94 papers (17 out of them were analyzed thoroughly) and, in particular among “indoor” pollutants, reported that VOCs could favor allergic and respiratory diseases by directing the immune system towards a Th-2 prevalence over the Th-1 function. These compounds have also been reported to facilitate Atopic Dermatitis (32).

A 2011 CBA controlled study in Korea has involved 51 children, with a mean age of 1.7 years, looking for an

association between Atopic Dermatitis symptoms and air quality. The authors created a low-pollution environment in the hospital: the rooms were built and decorated (paintings and furnishings) with low-pollution material, an air curtain was installed above the entrance and an air purifier-ventilator was put in the room. Patients were kept in this environment for an average of 3.3 days. Air quality was assessed every week by measuring: PM 2.5 and PM 10, formaldehyde, TVOC (benzene, toluene, ethylbenzene, xylene and styrene), CO, CO_2, NO_2, suspended bacteria and environmental mould. The quality of the ambient air was also evaluated in the rooms of the houses of each patient. In patients' home rooms the environmental factors studied were significantly higher in concentration than in the low-pollution hospital rooms, with the exception of benzene, toluene, ethylbenzene, xylene, CO and NO_2. The health of children improved during the days elapsed in the hospital and, when these children have been returned at home, 22 of them maintained the improvement regarding skin symptoms while the other 29 worsened. Among this group, the bedrooms of 2 children were newly repainted and for another 2 children wrapping paper was put on the walls. Moreover, 8 children among the group with worsened Atopic Dermatitis symptoms were hospitalised again, and consequently their health has improved again. This study has therefore shown that by placing children with AD in the appropriate home environment their health can improve (33).

Other authors reported similar results. Within an epidemiological study involving 2536 children exposed to paintings, floor coverings and new furniture before birth and in their first year of life, it has been found that the redecoration is related to allergic symptoms and 1.9 eczema (34).

A paper published in JACI has given an interesting interpretation on the onset of food allergy in children, which would depend on both skin barrier mutations and co-stimulating environmental factors (35). In this paper, researchers studied an experimental model in mice with mutation for filaggrin (analogous to the mutation studied in children with AD). These new-born mice were sensitized through the skin with food and environmental allergens such as Alternaria and Mites. In this way began the stimulation Th-2 that led to the AD and the anaphylactic reaction when the food was also introduced by mouth (and this in a more striking way in children of allergic mothers). On the other hand, when food was introduced by mouth before environmental skin sensitization, the anaphylactic reaction no longer appeared. This experimental study demonstrated the importance of two factors in inducing food allergy with skin manifestations (AD) or anaphylaxis: congenital skin barrier defect and stimulating environmental factors (food proteins, mites, Alternaria) (35). More studies are needed to demonstrate if the indoor pollutants reported in previous papers (31, 33, 34) could play a similar role.

PROACTIVE INITIATIVES TO REDUCE THE RISKS FROM AIR POLLUTION

Indoor air pollutants can cause many harmful effects. While further research is needed, understanding, and controlling common pollutants can help reduce the risk of indoor health concerns. Considering the potential risks of such substances also in the health of the fetus and infant, it is imperative that government agencies and organizations implement proactive measures to prevent potential adverse health outcomes. Today in many countries certifications exist to define Indoor Air Quality.

The Environmental Protection Agency (EPA), the executive agency tasked with environmental protection matters in the US, defines environmental justice (EJ) as "the fair treatment and meaningful involvement of all people (…) with respect to the development, implementation, and enforcement of environmental laws, regulations, and policies" (37).

EPA's Indoor Environments Division (IED) provides guidance and programs to help build the capacity of communities to understand and avoid indoor and outdoor health impacts.

European countries on the other hand are trying to tackle some of the sources of indoor air pollution by restricting the use of toxic substances or finding ways to reduce emissions. In Europe are emerging more and more restrictive requirements, both governmental and voluntary (**Table 5**). These requirements promote the development of low VOCs emitting paintings and are directly accepted as proof from programs for sustainable buildings.

Nevertheless, promoting new laws on this topic is not the only way to improve the quality of the air, but it is also necessary to increase perception in people, manufacturers, and builders on IAQ topics.

***Table 5**. Most relevant certifications regarding indoor air quality for paints and construction.*

Certification	Country/Institution	Application	Type	Ref.
Emission Level	France	Painting products	Compulsory	#39
CAM	Italy	Construction specification	Compulsory for public procurements	#40
Indoor airPLUS	EPA (USA)	Construction specification	Voluntary	#41
AgBB – ABG	Germany	Products for indoor use	Compulsory	#42
BREEAM	Building Research Establishment	Construction specification	Voluntary	#43
LEED	U. S. Green Building Council	Construction specification	Voluntary	#44

CONCLUSIONS

The Total Exposure Assessment Methodology (TEAM) Study of Environment Protection Agency in US has found levels of about dozen common organic pollutant to be 2 to 5 times higher inside homes than outside (38). VOCs and fine particles can play a role in allergy and respiratory diseases in children and in part they are due to the wall paints.

More studies are needed to explore the correlation between emissions resulting from painting walls and the possible effects on respiratory and allergic diseases in children (8) and taking in account the presence on the market of products with low VOCs, it is necessary to analyze the correlation between VOCs concentration in the paint with respiratory diseases.

In many cases the evidence is insufficient to arrive at firm conclusions therefore new high quality and observational studies, as well as clinical trials, on exposure to domestic VOCs and their effects on asthma/allergy would be necessary, despite the difficulties to find funds, participants, and to measure changes in indoor air composition and well-defined outcomes. A lot of work still remains to be done by color manufactures and wall paint industries to identify which chemicals have to be used more safely in the living environment of children, in order to reduce exposure to VOCs of children and adults with asthma and allergy.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests

The Authors have declared no conflict of interests.

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Conceptualization, draft, supervision: AB, GM. Check international medical databases: AB. Writing, tables, figures, review: AB, BZ, GM.

Ethical approval

Human studies and subjects

N/A.

Animal studies

N/A.

Data sharing and data accessibility

The data underlying this article are available in the article.

Publication ethics

Plagiarism

This is a review article and all original studies are cited as appropriate.

Data falsification and fabrication

All the data correspond to the real.

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